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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 16

Application Number: 09/586,156
Filing Date: 6/2/2000
Appellant(s): Arnold et al.,

Richard Aron Osman
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed on July 16,2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,807,522 Brown et al., 9-1998

Bates *et al.*, "Detection and kinetic studies of triplex formation by oligonucleotides using real-time biomolecular interaction analysis (BIA)." Nucleic Acids Research, vol. 23, no. 18 (1995), pp. 3627-3632.

Pease et al., "Light-generated oligonucleotide arrays for rapid DNA sequence analysis". Proc. Natl. Acad. Sci. USA, vol. 91 (May, 1994), pp. 5022-5026.

Tyagi *et al.*, " Molecular beacons: probes that fluoresce upon hybridization." Nature Biotechnology, vol. 14 (March, 1998), pp.303-308.

Anderson *et al.*, "Quantitative filter hybridization." Nucleic acid hybridization: a practical approach (1985), pp. 86-109, edited by Hames, BD and Higgins, JJ. Published by IRL Press Limited, P.O.Box 1, Eynsham, Oxford OX8 1JJ, England.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1, 2, 8, 11, 15, 16, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Bates *et al.*, (Nucleic Acids Res. 23, 3627-3632, 1995).

Claim 1 is drawn to a method for immobilizing a polynucleotide probe which comprises combining the probe with a polynucleotide target which polynucleotide target is stably associated with a surface of a solid support. In this method the polynucleotide probe and polynucleotide target are combined under conditions wherein the probe and target can and will

hybridize thereby immobilizing the probe. Also, in this method it is required that the probe or the target be double-stranded comprising complementary strands, while the other (i.e. probe or target) be single-stranded and comprise complementarity with one of the complementary strands.

Claim 15 is drawn to essentially the same method for immobilizing a polynucleotide probe as is recited in Claim 1 except in this embodiment it is required that the polynucleotide probe be double-stranded and that specific hybridization between target and probe be detected.

Bates *et al.*, teach detection and kinetic studies of triplex formation by oligodeoxynucleotides using real-time biomolecular interaction analysis (BIA). In this study, 5'-Biotinylated oligonucleotides were immobilized on the streptavidin-coated surface of a biosensor chip (page 3628, right column, first and second paragraphs). A single-stranded oligonucleotide (claim 22) immobilized on the chip surface was able to capture a DNA duplex by triplex recognition as described in claims 1 and 15. For example, Bt-T30 immobilized on the chip surface has been shown to capture of T30-A30 duplex (see second paragraph of left column in page 3629, fourth paragraph of left column in page 3630, Figure 4 and Figure 2 for sequences of oligonucleotides).

Regarding claims 8 and 16, two strands of the double stranded probe are noncovalently linked by Watson-Crick type of hydrogen pairing.

Regarding claims 11 and 23, the biosensor chip immobilized with 5'-Biotinylated oligonucleotides could be considered as a microarray (for definition of "microarray", see page 5 of the specification). Note that the definition suggests that any kind of solid support immobilized

with one kind of oligonucleotide (plurality of identical oligonucleotide) could be considered as oligonucleotide.

Therefore, Bates *et al.*, teach all limitations cited in claims 1, 2, 8, 11, 15, 16, 22, and 23.

Response to Arguments

I. In page 3, last paragraph bridging to page 4, first paragraph of the Brief on Appeal, appellant argued that: (1) "the structure requirements of our claims are neither met nor suggested by the cited Bates et al. (Nucleic Acids Res. 23, 3627-3632, 1995), which describes the entirely unrelated Hoogsteen triplex formation"since "there is no complementarity, as expressly required by our claims;" and (2) "note that even with Bates' polyT/polyA homopolymers, the orientation of the polyT probe binding is parallel (not complementary) with the polyA of the duplex (see Fig.2) and the polyA probe binding of the A30-A30-T30 triplex (p.3630) is antiparallel with the polyA-not with the polyT."

At page 6, third full paragraph of the Brief on Appeal, appellant asserts "[n]owhere described or suggested is the claimed solid phase hybridization assay involving triplex formation by hybridization between complementary targets and probes." This assertion directly contradicts appellants assertion regarding Hoogsteen triplex formation cited in the preceding paragraph (see the above arguments for the rejection under 35 U.S.C 102 (b)). Triplex formation involves Hoogsteen pairing between strands in addition to Watson-Crick pairing.

While appellant can selectively assert the absence or presence of a feature of his invention so as to attempt to avoid anticipation on the one hand and urge non-obviousness on the other it would appear unwise to do so when the claim at issue includes the feature.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the examiner agrees with appellant that the interaction between double stranded polyA/polyT and polyT was Hoogsteen binding. However, at least two types of hydrogen pairings exist in nucleic acid double helix, Watson-Crick type of hydrogen pairing and non-Watson-Crick interaction known as Hoogsteen pairing (see Bates et al., above). Since "complementary" or "complementarity" in the specification is defined as "the natural binding of polynucleotides under permissive salt and temperature conditions by base-pair" (see page 5, second paragraph), it is clear that appellant's definition of complementarity does not limit "complementarity" to Watson-Crick type of hydrogen pairing. Hoogsteen pairing between pyrimidine and purine can also be considered as complementary. Second, from the definition of "complementarity" in the specification (see above), it is clear that appellant's definition of complementarity does not limit to the orientation wherein the polyT probe binding is anti-parallel with the polyA of the duplex since there is no word "parallel" or "anti-parallel" in the definition. Third, since Bates *et al.*, did not teach a A30-A30-T30 triplex but taught a A30-T30-A30 triplex (see left column in page 3628 and right column in page 3630), appellant's interpretation to the reference of Bates *et al.*, is incorrect.

II. In page 4, footnote 1 of the Brief on Appeal, appellant argued that "we believe that complementarity limitation of our claim is unconditional" since " the action appears to rely on an untenable construction of our claims, construing the requirement of having complementarity" to mean merely having a potential to be complementary" or "capable of hybridizing with."

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. First, claim 1 recites that a single-stranded polynucleotide has complementarity with one strand of a double-stranded polynucleotide. Before the single-stranded polynucleotide hybridized with one strand of a double-stranded polynucleotide, single-stranded polynucleotide can be reasonably considered as "having a potential to be complementary" or "capable of hybridizing with" one strand of a double-stranded polynucleotide. Second, the rejection is not based on "having a potential to be complementary" or "capable of hybridizing with" (see above).

III. In page 4, footnote 2 of the Brief on Appeal, appellant argued that "Bates twice erroneously refers to a HD1-HD2•HD3 system" because "the reference system is called HD3-HD2•HD1" according to Bate's nomenclature since " HD3 is Hoogsteen bound to the HD2•HD1 duplex."

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. The examiner noted that the reference did describe a HD1-HD2•HD3 system (see right column in page 3630) or X-Y•Z triplet wherein X-Y interacted via Hoogsteen-type bonding and Y•Z was a Watson-Crick base pair but not HD3-HD2•HD1 system. Since one having ordinary skill in the art can use different nomenclatures to represent an identical DNA triplex, the nomenclature suggested by appellant (HD3-HD2•HD1) is no different from that used in the reference (HD1-HD2•HD3). There is no error in the reference.

2. Claims 1, 2, 8-13, and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.,* (Nature Biotechnology 14, 303-308, March 1996) in view of Pease *et al.,* (Proc. Natl. Acad. Sci. USA 91, 5022-5026, 1994).

Tyagi *et al.*, teach fluoresce upon hybridization using molecular beacons as probes (see page 304, Figure 1). These probes comprise covalently linked and non-covalently linked complementary strands with a hairpin structure as recited in claims 8, 9, and 16-18 (page 304, Figure 2) and undergo a spontaneous fluorogenic conformational change when they hybridize to their targets (page 303, abstract). Note that one of molecular beacon probes (molecular beacon A) used in this study consisted of a 15-nucleotide-long-probe sequence flanked by two complementary 5-nucleotide-long arm sequences and can therefore be considered as a double strand probe. The fluorophore, EDANS was joined to the 5'-terminal phosphate by a $-(CH_2)_6-S-CH_2-CO-$linker; and the quencher, DABCYL, was joined to the 3'-terminal hybroxyl group by a $-(CH_2)_7-NH-$linker.

Tyagi *et al.*, do not disclose a support with an immobilized oligonucleotide as described in claims 1 and 15 or a microarray with different immobilized oligonucelotides as described in claim 23.

Pease *et al.*, do teach light-generated oligonucleotide arrays for rapid DNA sequence analysis. In a preliminary experiment, Pease *et al.*, teach a 1.28 x 1.28 cm array of 256 different octanucleotides which was produced and hybridized with fluorescently labeled oligonucleotide probes.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have immobilized different stranded targets on a microarray as suggested by Pease *et al.*, and hybridized a single stranded target in the presence of a divalent cation using a probe with a structure of molecular beacons containing partial double strand

region wherein complementary strands are both covalently and noncovalently linked as suggested by Tyagi *et al.*. One having ordinary skill in the art would have been motivated to modify and combine the above methods together because the simple replacement of one well known type of hybridization probe, i.e. a molecular beacon, for another well known type of hybridization probe, i.e. a regular oligonucleotide, in a hybridization assay, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made. As regards the motivation to make the substitution cited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09. With regards to the limitation in claims 12 and 13 wherein the conditions include an amount of a metal ion sufficient to enhance hybridization of the target and probe, Tyagi *et al.*, teach that Mg^{2+} is critical to form a stable stem hybrid in the molcular beacon (see page 305, left column, first paragraph). Therefore, it would have been routine for one having ordinary skill in the art at the time the invention was made to perform the hybridization assay in the presence of divalent cations since divalent cations interact electrostatically with negative charges of DNA and stabilize duplex DNA by decreasing the electrostatic repulsion between the two strands of the duplex.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

3. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (March 1996) in view of Pease *et al.*, (1994) as applied to claim 1 above, and further in view of Anderson *et al.*, (Nucleic Acid Hybridization: a practical approach, edited by Hames & Higgins, pages 86-109, 1985).

Tyagi *et al.*, in view of Pease *et al.*, teach all of the limitations of claim 3 as argued above against claim 1, except these authors do not teach releasing the immobilized probe from the solid support following hybridization. However, Anderson *et al.*, do teach the reuse of a solid support and /or probe following hybridization by removal of the immobilized probe from a solid support (see for example, page 109). Therefore, it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the teachings of Tyagi *et al.*, in view of Pease *et al.*, wherein the immobilized probe is removed from the solid support following hybridization. The ordinary artisan would have been motivated to make this modification in order to reuse the solid support and/ or the probe in subsequent experiments as suggested by Anderson *et al.*, thereby reducing laboratory expenses.

4. Claims 14 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi *et al.*, (1996) in view of Pease *et al.*, (1994) as applied to Claim 1 and 15 above and further in view of Brown *et al.*, (US Patent No. 5,807,522, filed on June 7, 1995).

Tyagi *et al.*, in view of Pease *et al.*, teach all of the limitations of claims 14 and 24 as argued above against claims 1 and 15, except these authors do not teach that their solid support comprise a polycationic surface as recited in claims 14 and 24. However, Brown *et al.*, teach a

solid support comprising a polycationic surface as well as the fabrication and the advantages thereof (see for example, columns 13, 16, and 18).

Therefore, it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the teaching of Tyagi et al., in view of Pease et al., wherein their solid support comprise a polycationic surface as taught by Brown et al.. The motivation to make the substitution combination recited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09. Furthermore, the substitution of one known reagent with known properties for a second well known reagent with known properties is routine in the art.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 5, second paragraph, to page 7, third paragraph of the Brief on Appeal, appellant argued that: (1) Tyagi *et al.*, " neither discloses nor suggests anything about the claimed duplex hybridization method" since "Tyagi relies on conventional single stranded-single strand hybridization" and only "single stranded component (here, the target) have complementarity with one of the strands of the double-stranded component (here, the probe);" (2) "nowhere described or suggested is the claimed solid phase hybridization assay involving triplex formation by

hybridization between complementary targets and probe;" and (3) " though Tyagi's probes can exist in a partially-double stranded form, they are not double-stranded when hybridized to target."

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, the molecular beacon probe taught by Tyagi *et al.*, is a partial double stranded probe, not a single stranded probe. Second, in the reference of Tyagi *et al.*, besides "single stranded component (here, the target) have complementarity with one of the strands of the double-stranded component (here, the probe)", the single stranded target also has complementarity with at least one base of one of the strands of the double-stranded component of probe (AGCG/TCGC, see Figure 2 in page 304). Note that claim 1 does not require that single stranded component have full complementarity with one of the strands of the double-stranded component (also see the definition of "complementarity" in page 5 of the specification). Third, the examiner notes that claim 1 does not contain the limitation that the part of the probe bound to the target must be from the double-stranded component of the probe. Fourth, in response to appellant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., triplex formation and probe is still double when hybridized to target) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For the above reasons, it is believed that the rejections should be sustained.

Respectively submitted,

Frank Lu
September 26,. 2001

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